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Enantioselective Total Synthesis of Macfarlandin C, a Spongian Diterpenoid Harboring a Concave-Substituted *cis*-Dioxabicyclo[3.3.0]octanone Fragment

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In memory of Ronald C. D. Breslow

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Abstract: The enantioselective total synthesis of the rearranged spongian diterpenoid (–)-macfarlandin C is reported. This is the first synthesis of a rearranged spongian diterpenoid in which the bulky hydrocarbon fragment is joined via a quaternary carbon to the highly hindered concave face of the *cis*-2,8-dioxabicyclo[3.3.0]octan-3-one moiety. The strategy involves a late-stage fragment coupling between a tertiary carbon radical and an electrophilic butenolide resulting in the stereoselective formation of vicinal quaternary and tertiary stereocenters. A stereoselective Mukaiyama hydration that orients a pendant carboxymethyl side chain *cis* to the bulky octahydronaphthalene substituent was pivotal in fashioning the challenging concave-substituted *cis*-dioxabicyclo[3.3.0]octanone fragment.

A diverse group of marine diterpenoids are believed to arise by fragmentation and rearrangement of the steroid-like spongian skeleton.^[1] A distinctive set of these rearranged spongian diterpenoids harbor a *cis*-2,8-dioxabicyclo[3.3.0]octan-3-one fragment (**1**) attached at C-6 to a quaternary carbon of a hydrophobic fragment (Figure 1). These diterpenoids can be further subdivided into two families that differ by the orientation of the hydrocarbon fragment. In the largest collection, the hydrocarbon moiety resides on the more sterically hindered concave face of the *cis*-dioxabicyclo[3.3.0]octan-3-one fragment, exemplified by macfarlandin C (**2**),^[2] whereas cheloviolene A (**3**)^[3] is representative of members in which the hydrocarbon unit resides on the convex face.

Our interest in these structures was initially piqued by Sütterlin's observations of the unique Golgi-altering activity of macfarlandin E, a structurally related diterpenoid in which the *cis*-dioxabicyclooctanone fragment is replaced by a 2,7-dioxabicyclo[3.2.1]octan-3-one subunit.^[4] Macfarlandin E, and some simplified congeners having either a *cis*-2,8-dioxabicyclo[3.3.0]octan-3-one or a 2,7-dioxabicyclo[3.2.1]octan-3-one subunit, uniquely induce irreversible fragmentation of the Golgi apparatus with retention of fragments in the pericentriolar region of the cell.^[4,5] The fused and bridged dioxabicyclooctanone moieties degrade in the presence of primary amine functionalities to form pyrrole products via putative 1,4-dialdehyde intermediates.

This mode of conjugation is suggested to be important for the Golgi phenotype of these natural products.^[4–6]

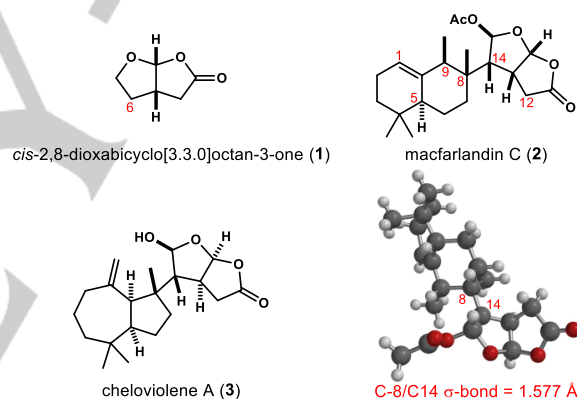
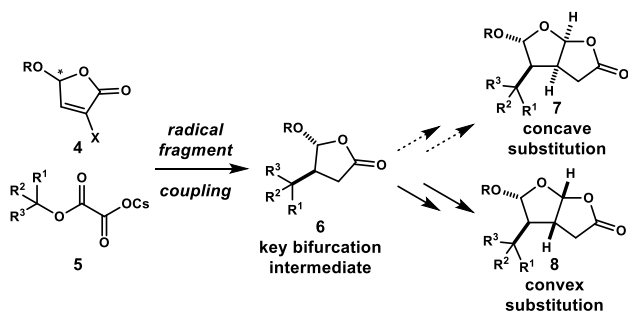


Figure 1: Rearranged spongian diterpenoids harboring the *cis*-2,6-dioxabicyclo[3.3.0]octan-3-one moiety, and a ball-and-stick representation of the X-ray model of macfarlandin C showing the unusually long C-8/C-14 σ -bond linking the two chiral fragments.

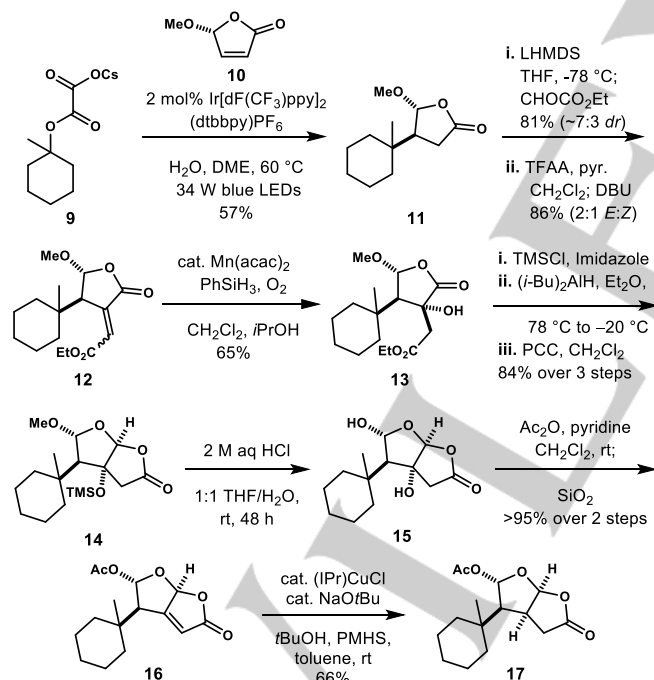
The central challenge in the synthesis of the marine diterpenoids exemplified in Figure 1 is fashioning the σ -bond that links the two chiral fragments in a stereocontrolled fashion. This challenge is heightened significantly in members such as macfarlandin C (**2**) wherein the bulky hydrocarbon unit resides on the sterically demanding concave face of *cis*-2,8-dioxabicyclooctanone fragment. This steric congestion is apparent in the X-ray model of macfarlandin C (Figure 1),^[2] and strikingly illustrated in the unusually long length (1.577 Å) of the C-8/C-14 σ -bond that joins the two fragments. In contrast, this bond in cheloviolene A (**3**) is quite standard (1.546 Å).^[3a,7] In addition, this steric congestion results in significant distortion of the *cis*-2,8-dioxabicyclooctanone fragment of macfarlandin C (**2**) as compared to that of cheloviolene A (**3**).^[7]

When we initiated studies to develop a chemical synthesis of macfarlandin C (**2**), only the related structural archetypes cheloviolene A (**3**) and cheloviolene B having the hydrocarbon fragment positioned on the convex face of the *cis*-2,8-dioxabicyclo[3.3.0]octan-3-one unit had been synthesized.^[8] The



Scheme 1: General and divergent approach to 6-substituted *cis*-2,8-dioxabicyclo[3.3.0]octan-3-ones.

approach employed in these syntheses to access the 6-substituted *cis*-2,8-dioxabicyclo[3.3.0]octan-3-one moiety relied on the coupling of a tertiary radical with a 5-alkoxy butenolide.^[9] Although this approach allowed for facile access to diterpenoids bearing the C-6 hydrophobic fragment on the convex face of the *cis*-2,8-dioxabicyclo[3.3.0]octan-3-one unit, we were unable to tune this coupling to access the alternate stereoisomer.^[8b] We report herein the development of a synthetic approach to *cis*-2,8-dioxabicyclo[3.3.0]octan-3-ones attached at C-6 to a quaternary carbon of a bulky hydrophobic fragment that allows for the divergent synthesis of either C-6 substituted stereoisomer from the product of fragment coupling (Scheme 1). The utility of this strategy is exemplified by the enantioselective total synthesis of (–)-macfarlandin C (**2**).



Scheme 2: Model studies toward accessing concave 6-substituted *cis*-2,8-dioxabicyclo[3.3.0]octan-3-one **17**. (dF(CF₃)ppy = 2-(2,4-difluorophenyl)-5-trifluoromethylpyridine, dtbbpy = 4,4'-di-*t*-Bu-2,2'-bipyridine, DME = dimethoxyethane, THF = tetrahydrofuran, LHMDS = lithium hexamethyldisilazide, TFAA = trifluoroacetic anhydride, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, acac = acetylacetonate, TMSCl = chlorotrimethylsilane, PCC = pyridinium chlorochromate, lpr = 1,3-bis(2,6-diisopropylphenyl)-1,3-dihydro-2H-imidazol-2-ylidene, PMHS = polymethylhydrosiloxane).

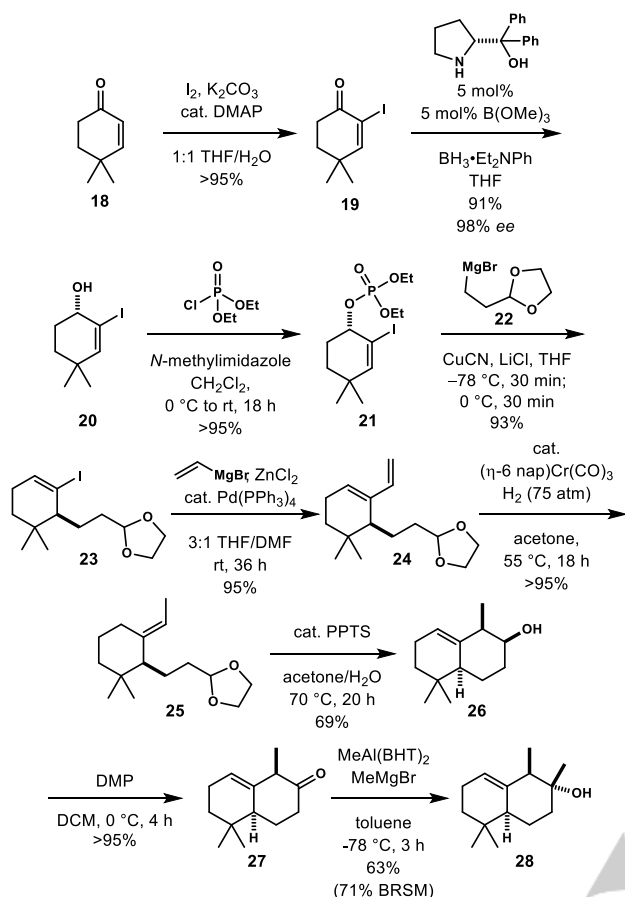
We initiated exploratory model studies with lactone **11**, which is readily available from the coupling of cesium oxalate **9** and 5-methoxybutenolide (**10**).^[8b] Our original aim was to explore

the feasibility of directly installing a carboxymethyl substituent *cis* to the bulky 1-methylcyclohexyl substituent of **11**. This goal has proven to be exceptionally challenging and has not yet been realized. One approach we examined was to introduce the side chain as an alkylidene fragment, with the hope that the double bond could be reduced selectively from the face anti to the adjacent hydrocarbon side chain. Aldol reaction of lactone **11** with ethyl glyoxylate yielded a mixture of aldol adducts, which was dehydrated to provide in high overall yield alkylidene product **12** as a mixture of *E* and *Z* stereoisomers. Unfortunately, under no conditions that we examined was the stereoisomeric hydrogenation product having the 1-methylcyclohexyl and carboxymethyl substituents *cis* formed selectively. Among the conditions examined were heterogeneous catalytic hydrogenation using Pd, Pt and Rh catalysts, homogeneous hydrogenation using Rh or Ir catalysts, Cu and Ni-promoted hydride reduction,^[10] and several recent and older hydrogenation methods that likely proceed by initial hydrogen atom transfer.^[11,12]

We turned to a strategy in which the ester side chain would be “locked” into a *cis* relationship with the bulky hydrophobic substituent by incorporation of a hydroxyl group at the α-position of a butyrolactone intermediate.^[13] Mukaiyama hydration of alkylidene lactone **12** took place with complete regioselectivity from the lactone face opposite the 1-methylcyclohexyl substituent to give alcohol intermediate **13**.^[14–16] The transformation of alcohol **13** to concave-functionalized *cis*-2,8-dioxabicyclo[3.3.0]octan-3-one **17** was initially accomplished by way of three isolated intermediates. After initial silyl protection of the hydroxyl substituent, reaction with excess (*i*Bu)₂AlH provided a mixture of lactol epimers, which were directly oxidized to give *cis*-dioxabicyclooctanone **14** in high yield.^[8b] Hydrolysis of **14** at room temperature in dilute HCl furnished diol **15**, which was then allowed to react with excess acetic anhydride at room temperature. The intermediate diacetate, which could be observed in the crude product by NMR analysis, converted completely to elimination product **16** by simple treatment with silica gel. Conjugate-silane reduction of this unsaturated lactone by the method of Buchwald then provided *cis*-2,8-dioxabicyclo[3.3.0]octan-3-one **17** in good yield.^[17]

Our application of this strategy to construct (–)-macfarlandin C (**2**) is summarized in Schemes 3 and 4. The route commences with the enantioselective synthesis of octahydronaphthalene tertiary alcohol **28** in nine steps from 4,4-dimethylcyclohexen-1-one (**18**). Iodination of **18**, followed by catalytic enantioselective reduction of α-iodocyclohexenone **19** by a variant of the Corey-Bakshi-Shibata reduction afforded (*S*)-cyclohexenol **20** in high yield and 98% ee.^[18,19] After conversion to allylic phosphate **21**, *anti*-S_N2' allylic displacement by reaction with an excess of the organocuprate intermediate generated *in situ* from CuCN and Grignard reagent **22** gave vinyl iodide **23** in high yield.^[19] Enantioselective HPLC analysis showed that the displacement took place with complete transfer of chirality.

As a prelude to forming the (*E*)-ethylidene side chain that is required for the pivotal intramolecular ene cyclization to fashion the octahydronaphthalene fragment,^[20] iodide **23** was advanced by Negishi vinylation to diene **24**.^[21] Exposure of **24** to 75 atm of hydrogen in the presence of catalytic (η⁶-naphthalene)chromium tricarbonyl occasioned selective delivery of hydrogen to the termini of the diene to give exclusively the (*E*)-ethylidene product **25** in 95% yield from vinyl iodide **23**.^[22] Treatment of this unsaturated acetal with catalytic PPTS in aqueous acetone at

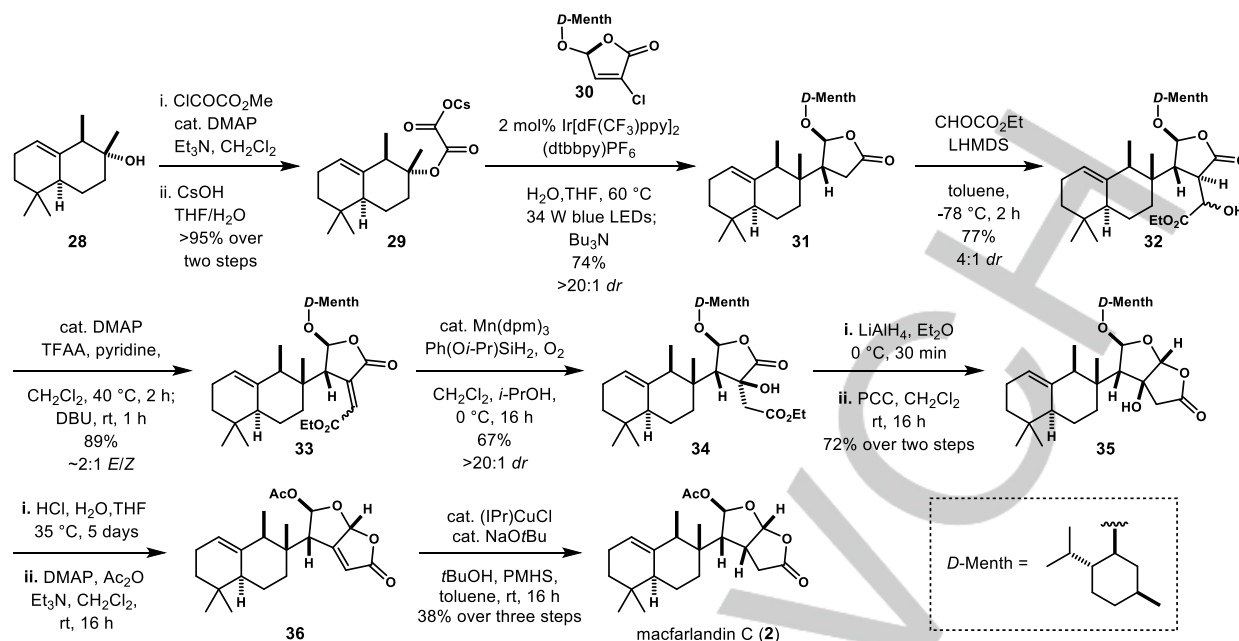


Scheme 3: Enantioselective construction of octahydronaphthalene oxalate coupling partner **28**. (DMAP = *N,N*-dimethyl-4-aminopyridine, DMF = *N,N*-dimethylformamide, PPTS = pyridinium *para*-toluenesulfonate, DMP = Dess-Martin periodinane, BHT = 2,6-di-*tert*-butyl-4-methylphenol).

70 °C promoted stereoselective intramolecular carbonyl-ene cyclization of the corresponding aldehyde to give alcohol **26** harboring the octahydronaphthalene core of macfarlandin C in 69% yield.^[20,23] The secondary alcohol of **26** was then oxidized using Dess-Martin periodinane to ketone **27**,^[24] which was transformed

with high selectivity to equatorial tertiary alcohol **28** upon sequential treatment with an excess of Yamamoto's MAD reagent (methylaluminum bis(2,6-di-*tert*-butyl-4-methylphenoxide) and methylmagnesium bromide.^[25]

The pivotal fragment coupling step and advancement of the coupled product in eight steps to (–)-macfarlandin C are summarized in Scheme 4. Alcohol **28** was converted first to the oxalate radical precursor **29** by sequential reaction at room temperature with methyl chlorooxalate and cesium hydroxide. Irradiation of a solution of oxalate salt **29**, *D*-menthol-derived chlorobutenolide **30**,^[8] and 2 mol% of the iridium photocatalyst with high-intensity blue LEDs for 20 h at 60 °C, followed by addition of excess tri-*n*-butylamine and irradiation for an additional 6 h gave coupled product **31** in 74% overall yield from alcohol **28**.^[26,27] This product was then advanced in high yield to vinylogous β-alkoxyacyl ester **33** by the aldol-dehydration sequence developed in our earlier model studies (Scheme 2). Mukaiyama hydration of **33** proceeded with high regio- and stereoselectivity to deliver alcohol intermediate **34**, leaving the electron-rich trisubstituted double bond untouched. The highest yields in this conversion were realized using the more active catalytic system reported by Shenvi.^[28] To our surprise, α-hydroxy lactone **34**, and alcohol-protected variants thereof, proved remarkably resilient to reduction by a variety of hydride reagents. Fortunately, reaction with a large excess of lithium aluminum hydride at 0 °C gave rise to a mixture bicyclic lactols, which upon direct oxidation with excess PCC provided dioxabicyclooctanone **35** in 72% yield. Without purification of intermediates, the menthoxy group was removed under acidic conditions, the resulting diol product was peracetylated and then exposed to DMAP to provide butenolide intermediate **36**. Silane reduction promoted by a *N*-heterocyclic-carbene copper complex^[17] then delivered (–)-macfarlandin C (**2**) in 38% yield over three steps. Spectroscopic properties and optical rotation of synthetic (–)-macfarlandin C (**2**) are indistinguishable from those reported for the dorid nudibranch isolate.^[2]



Scheme 4: Photoredox-mediated fragment coupling for the generation of lactones **31** and elaboration to macfarlandin C (**1**). (DMAP = *N,N*-dimethyl-4-aminopyridine, dF(CF₃)ppy = 2-(2,4-difluorophenyl)-5-trifluoromethylpyridine, dtbbpy = 4,4'-di-*t*-Bu-2,2'-bipyridine, LHMDS = lithium hexamethyldisilazide, TFAA = trifluoroacetic anhydride, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, dpm = dipivaloylmethane, PCC = pyridinium chlorochromate, PMHS = polymethylhydrosiloxane).

In summary, the first total synthesis of rearranged spongian diterpenoids having a bulky hydrocarbon positioned on the highly congested concave face of the *cis*-2,8-dioxabicyclo[3.3.0]octan-3-one fragment is reported. This sequence was exemplified in the first total synthesis of the structurally elaborate diterpenoid (–)-macfarlandin C (**2**), an enantioselective synthesis that rigorously establishes the absolute configuration of the natural product, which previously had been proposed only on the basis of biosynthetic conjecture. Three transformations are critical to the successful synthesis of **2**: a) stereoselective carbonyl-ene cyclization to fashion the octahydronaphthalene fragment, b) high-yielding fragment coupling between a tertiary alcohol-derived tertiary radical and an electron-deficient alkene resulting in the formation of a new quaternary and tertiary stereocenters, and c) a stereo- and diastereoselective Mukaiyama hydration that allows the concave-substituted *cis*-2,8-dioxabicyclo[3.3.0]octan-3-one unit to be elaborated from the product of fragment coupling.

Acknowledgements

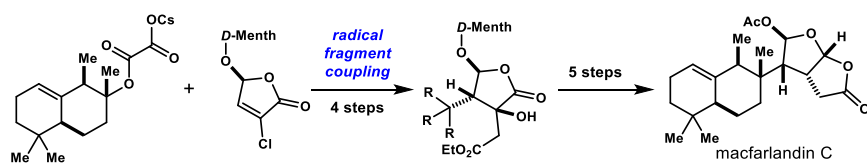
Financial support was provided by the National Science Foundation (CHE-1265964 and CHE-1661612) and the National Institute of General Medical Sciences (R01-GM098601). We thank the ACS Organic Chemistry Division for partial support of G.L.L. by a Graduate Fellowship and the German Academic Exchange Service (DAAD) for postdoctoral fellowship support of A.P.D. NMR and mass spectra were determined at UC Irvine using instruments purchased with the assistance of NSF and NIH shared instrumentation grants. We are grateful to Eloisa Serrano and Yuriy Slutskyy for studies of alternate approaches to these targets.

Keywords: C–C coupling • natural product synthesis • photoredox chemistry • terpene synthesis • radical chemistry

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